REMARKS

The Official Action dated June 8, 2005 and references cited therein have been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Status of the prosecution:

Claims 1, 2, 4-14 and 16-23 are pending. The Action notes that a previous amendment of the claims to recite "cDNA" instead of "DNA" overcomes an objection to the claims made in the December 7, 2004 Official Action. The claims remain objected to, but it is suggested that the same amendment to the phrases in step (b) and step (c) of claims 1 and 14, would overcome that objection. The claims have been amended to recite "cDNA" in the appropriate phrases. Applicants respectfully submit that the objection to the claims should now be overcome.

The rejection of claims 13, 14, 20 and 21 under 35 U.S.C. §112, second paragraph, made in the December 7, 2004 Official Action has been withdrawn in view of the amendments made in Applicants' reply mailed April 7, 2005.

The rejection of claims 1, 2, 4, 5, 7-14 and 16-23 under 35 U.S.C. §103(a), as allegedly unpatentable over Mack et al. in view of Gu et al., made in the December 7, 2004 Official Action has been withdrawn in view of the amendments made in Applicants' reply mailed April 7, 2005.

Claims, 1, 2, 4-14 and 16-23 stand newly rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness on the following grounds: (1) claims 1 and 14 for the phrase "transcribing resultant amplified DNA into cRNA" in step (c); (2) claims 2 and 4-13, and claims 16-23, by way of dependence from claim 1 and claim 14, respectively; and (3) claims 4 and 12 in the recitation of "said conditions," while being dependent on claim 1, which recites more than one set of conditions.

Claims 1, 2, 4-14 and 16-23 stand newly rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Mack et al. in view of Kong et al. (U.S. Patent No. 5,814,506,

issued September 29, 1998) as evidenced by McLaughlin et al. (U.S. Patent No. 6,783,940, filed October 31, 2001, issued August 31, 2004).

Current amendments to the claims and/or specification:

Claims 1, 4, 6, 12 and 14 have been amended to further clarify the subject matter of the present invention. No new matter has been added. The amendments are intended for clarification, and do not narrow the scope of the claims in any way. Applicants submit that the currently amended claims are in condition for allowance, as they satisfy all formal requirements and are directed to novel and nonobvious subject matter. Support for Applicants' position is set forth below.

The claims meet the requirements of 35 U.S.C. §112, second paragraph:

Claims 1 and 14, and claims dependent therefrom, were deemed indefinite for recitation of the phrase "transcribing resultant amplified DNA," or "contacting amplified DNA." The claims have been amended to recite "double stranded cDNA" in those phrases. Accordingly, this ground of rejection should be overcome.

Claims 4 and 12 were deemed indefinite in the recitation of "said conditions," while being dependent from claim 1. Those claims have been amended to specify that "said conditions" are the conditions of the second strand cDNA synthesis step as recited in claim 1. Support for the amendment may be found in the specification at page 14, lines 3-5. Accordingly, this ground of rejection also should be overcome.

Applicants submit that the claims as amended satisfy all requirements of 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of the rejection therefore is requested.

The claimed subject matter is not obvious over the teachings of the cited art:

Claims 1, 2, 4-14 and 16-23 stand rejected under 35 U.S.C. §103(a) as unpatentable over the teachings of Mack et al. (Mack) in view of the teachings of Kong et al. (Kong), as evidenced by the teachings of McLaughlin et al (McLaughlin). Applicants traverse this rejection.

Claims 1 and 14, and claims dependent therefrom, are directed to a method for amplifying at least one mRNA in a sample containing a plurality of different mRNAs or to a method for comparing the presence or amount of at least one mRNA of interest in a first sample and in a second sample, the first sample and the second sample each containing a plurality of different mRNAs from one or more cells. In the method, the first step (reverse transcription) is carried out under standard conditions, but the second strand synthesis is carried out at an elevated temperature (45-80°C) using the thermostable DNA polymerase, specifically the Bst large fragment DNA polymerase, and a thermostable RNAse H. An advantage flowing from the claimed invention as a whole is that use of the elevated temperature and thermostable enzymes in the second strand synthesis results in the generation of relatively large amounts of RNA from a small starting number of cells with high efficiency, and in a substantially reduced time period compared to known methods for performing RNA amplification (Specification at page 5, lines 4-8).

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the examiner to provide a reason why one of ordinary skill in the art would have been motivated to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from Applicants' disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). For the reasons discussed below, a proper *prima facie* case of obviousness has not been set forth.

The Examiner alleges that it would have been obvious to the skilled artisan to substitute another well known DNA polymerase, such as Bst large fragment DNA polymerase, for the *E.coli* polymerase taught by Mack, and further within the purview of the skilled artisan to optimize conditions to accommodate the selected well known DNA polymerase. This analysis falls short because the claimed methods do not merely call for the substitution of one DNA polymerase for another. Rather, as outlined above, the claimed methods improve over the art by utilizing an elevated temperature and thermostable polymerases in the second strand DNA synthesis step. The selection of Bst large fragment

DNA polymerase is made to accommodate the elevated temperature, not *vice versa* as alleged by the examiner. This clear departure from standard cDNA synthetic procedures allows for improved production of cRNA following the subsequent transcription step, as discussed above.

The claims have been amended to emphasize the inventive aspects of the second strand DNA synthesis step. Applicants maintain that the skilled artisan would not have been motivated to combine the cited references to arrive at the invention as presently claimed. The Examiner cites the MPEP to support the notion that the test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in art. Applicants do not argue that the measure of obviousness includes all that properly combined references teach; however, there must an initial motivation to combine the references. As the Board of Appeals recently stated in *Ex parte Gottling* (B.P.A.I. 2005):

> Obviousness cannot be established by combining prior art to produce the claimed invention absent some teaching or suggestion supporting the combination. The mere fact that the prior art may be modified in the manner suggested by an examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

Here, as in that case, because none of the cited references specifically recognizes the advantages of the methods disclosed and claimed in the present application, there can be no suggestion in the prior art itself as to the desirability of modifying the teachings of one reference with those of the others. Indeed, none of the cited references is concerned in any way with improving on the amount of RNA produced in an RNA amplification, much less in accomplishing such an improvement by modifying cDNA synthesis. While Mack teaches a standard RNA amplification process in an example, Mack *as a whole* is focused not on the improvement of such reactions, but rather on methods of exploiting a biological target, CZA8, in the diagnosis, prognosis and treatment of breast or colorectal cancer. Therefore, Mack cannot be said to provide any motivation to modify a standard RNA amplification reaction to provide improved RNA production.

Kong does not provide the teaching or motivation so clearly absent from Mack. Kong teaches the cloning and production of Bst large fragment DNA polymerase. Kong further

teaches that thermostable polymerases are useful for PCR methods (Col. 1, lines 63-67), which requires thermal cycling, and further that Bst large fragment DNA polymerase is useful for DNA sequencing (Col. 2, lines 3-4), wherein sequencing reactions performed at high temperatures melt secondary structure, resulting in uniform band intensities and low background (Col. 2, lines 6-10). Kong makes no mention whatsoever of cDNA synthesis, much less of Bst DNA polymerase being useful for cDNA synthesis. Therefore, Kong cannot be said to provide any hint or suggestion that would motivate combining its teachings with those of Mack to arrive at the presently claimed invention.

McLaughlin is directed to improving PCR by reducing non-specific amplification. Because McLaughlin teaches PCR methods, McLaughlin of course teaches thermostable polymerases in the column bridging columns 2 and 3, as the examiner notes. However, McLaughlin nowhere teaches that thermostable polymerases would have any utility outside the thermal cycling reactions that define PCR. McLaughlin nowhere mentions cDNA synthesis, and therefore certainly provides no hint or suggestion that thermostable enzymes would be useful in cDNA synthesis, and most certainly does not hint or suggest that an improvement in cDNA synthesis would in any way improve on an RNA amplification reaction. Therefore, McLaughlin does not evidence any knowledge of the skilled artisan that would motivate the modification of Mack's teachings, or the teachings of Mack and Kong combined, to arrive at the claimed invention.

It is clear from the foregoing that none of the cited references themselves provide any hint or suggestion that would have motivated the skilled artisan to combine their teachings to arrive at the claimed methods, particularly with respect to modifying second strand cDNA synthesis to improve on the ultimate output of an RNA amplification process. Any combination in the absence of a "specific hint or suggestion in a particular reference" is thus necessarily the result of impermissible hindsight and is not a proper basis for a *prima facie* of obviousness. *In re Sang Su Lee,* 277 F.3d 1338 (Fed. Cir. 2002).

For the reasons set forth above, Applicants respectfully assert that a *prima facie* case of obviousness on the basis of the cited references has not been established. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) is therefore requested.

Conclusion:

In view of the claim amendments submitted herewith and the foregoing remarks, the presently-pending claims are believed to be in condition for allowance. Applicants respectfully request early and favorable reconsideration and withdrawal of the rejections set forth in the June 8, 2005 Action, and allowance of this application.

Respectfully submitted,

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